Presentation, diagnostic assessment and surgical outcomes in primary hyperparathyroidism

Title:

Presentation, diagnostic assessment and surgical outcomes in primary hyperparathyroidism: a single centre's experience

Running title:

Investigations and outcomes in PHPT

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Summary

Objective: Primary hyperparathyroidism (PHPT) is a common reason for referral to endocrinology but the evidence base guiding assessment is limited. We evaluated the clinical presentation, assessment and subsequent management in PHPT.

Design: Retrospective cohort study.

Patients: PHPT assessed between 2006 – 2014 (n = 611) in a university hospital.

Measurements: Symptoms, clinical features, biochemistry, neck radiology and surgical outcomes.

Results: Fatigue (23.8%), polyuria (15.6%) and polydipsia (14.9%) were associated with PHPT biochemistry. Bone fracture was present in 16.4% but was not associated with biochemistry. A history of nephrolithiasis (10.0%) was associated only with younger age (P = 0.006) and male gender (P = 0.037). Thiazide diuretic discontinuation was not associated with any subsequent change in calcium (P = 0.514). Urine calcium creatinine clearance ratio (CCCR) was <0.01 in 18.2% of patients with confirmed PHPT. Older age (P < 0.001) and lower PTH (P = 0.043) were associated with failure to locate an adenoma on ultrasound (44.0% of scans). When an adenoma was identified on ultrasound the lateralization was correct in 94.5%. Non-curative surgery occurred in 8.2%

and was greater in those requiring more than one neck imaging modality (OR 2.42, P = 0.035).

Conclusions: Clinical features associated with PHPT are not strongly related to biochemistry. Thiazide cessation does not appear to attenuate hypercalcaemia. PHPT remains the likeliest diagnosis in the presence of low CCCR. Ultrasound is highly discriminant when an adenoma is identified but surgical failure is more likely when more than one imaging modality is required.

Keywords

Hyperparathyroidism, primary; Calcium, Hypercalcemia; Thiazides; Vitamin D; Parathyroid Hormone; Hyperparathyroidism

Introduction

Primary hyperparathyroidism (PHPT) is a common endocrine condition with a prevalence of 0.1-1%, a female preponderance and a strong association with ageing[1,2]. In the modern era, PHPT is often detected incidentally through routine biochemical testing and is, in this milder form, often described as asymptomatic, in distinction from more severe PHPT associated with classical bone, renal and neuropsychiatric manifestations. Many patients with relatively modest hypercalcaemia will report symptoms that are potentially attributable to PHPT. However, the degree to which these correlate with biochemical markers of severity and their reversibility with surgical cure remains unclear[3]. The majority of PHPT may remain undiagnosed as suggested by a recent study which identified measurement of parathyroid hormone (PTH) in only 31% of hypercalcaemic patients[4]. In recent years the normocalcaemic variant of PHPT has gained increasing recognition, although this is beyond the scope of our investigation[5].

Guidance on the assessment and management of PHPT comes from the 4th International Workshop on PHPT. This emphasises the importance of securing the diagnosis of PHPT before considering whether surgical intervention is appropriate (a decision largely based on age, serum calcium, and presence of bone and/or renal complications)[6]. Only when a decision to pursue surgical cure is made should neck imaging be performed. However the optimal imaging modality in this context remains unclear and in a small but important minority of cases, the source of PTH excess remains elusive despite multiple imaging. The

international workshop recognises the value of neck imaging by ultrasound, ^{99m}Tc-sestamibi and CT in pre-operative localization[7], but does not specify an optimal approach.

Familial Hypocalciuric Hypercalcaemia (FHH) is an important differential diagnosis to exclude in patients with apparent PHPT as it is often associated with mild hypercalcaemia and PTH concentrations which overlap with the lower end of those observed in PHPT. The initial recommended screening test to exclude FHH, in addition to a full family history, is the urine calcium creatinine clearance ratio (CCCR), which should be > 0.01 in patients with PHPT[8]. Another potential contributor to hypercalcaemia in patients with probable PHPT is thiazide diuretic use, although recent reports suggest the impact to be minimal and paradoxically thiazides may even reduce blood PTH concentrations[9].

We have collated one of the largest cohorts of patients presenting for specialist endocrine assessment of PHPT, characterised in detail with respect to demographics, clinical features, biochemistry, imaging, surgery, pathology and subsequent outcomes. We sought to utilise this resource to address the relationship between presenting features and biochemical indices of PHPT; assess the discriminatory value of CCCR; determine the frequency of delayed diagnosis of PHPT; determine factors associated with the decision to pursue surgery; assess the effectiveness of pre-surgical neck imaging in a 'real world' context and relate these findings to surgical outcomes.

Materials and Methods

Patients

All patients presenting with a new diagnosis of PHPT (n = 611) to Edinburgh Centre for Endocrinology & Diabetes clinics (Royal Infirmary of Edinburgh & Western General Hospital) between 2006 and 2014 were identified from our comprehensive clinic database. Patients presenting following family screening for genetic causes of PHPT were excluded from this cohort but all index cases were included. Basic demographic details were obtained from electronic patient records. Social deprivation status was assessed using the 'Scottish Index of Multiple Deprivation' (SIMD 2016), which assigns individuals a rank from 1 (most deprived) to 6976 (least deprived) based on postcode[10]. Symptoms at presentation and other clinical features were gleaned from letters pertaining to PHPT in the electronic patient record. Ethical approval for this project was not required as it involved only retrospective review of our own patient cohort.

Biochemistry

Calcium (plasma and urine), phosphate, magnesium, alkaline phosphatase and creatinine were measured by standard laboratory methods. Adjusted calcium was derived using the following calculation: [calcium] + ((40 - [albumin]) x 0.02). Peak calcium was defined as the highest ever recorded calcium (from data available 1999 – 2016). CCCR was obtained either from spot urine sample or 24 hour urine collection, in association with contemporaneous plasma samples, using the following calculation: ([urine calcium (mM)] x ([serum creatinine

(μM)] x 1000)) / ([serum calcium (mM)] x [urine creatinine (mM)]). Patients were not on thiazide diuretics or calcium supplementation prior to urine collection. Three PTH assays were used across the 9 years of patient acquisition, all of which measured 'intact' 1-84 PTH: the Abbott Architect i2000 chemiluminescent microparticle-enhanced immunoassay (50.6%), the Siemens Immulite 2000 solid-phase 2-site chemiluminescent enzyme linked immunometric assay (36.0%) and the Roche Cobas E411 electrochemiluminescent assay (13.4%). All reported PTH values were normalised to the Abbott Architect i2000 assay using regression equations (from locally derived comparison data). Vitamin D was measured using LC-MS/MS; deficiency was defined as <25nM and insufficiency as 25 – 50nM. Biochemical results dating back to 1999 were available on our system and were interrogated to identify the interval between a first hypercalcaemic result and the first assessment of PTH, as a proxy of delayed diagnosis.

Imaging

The standard sequence of imaging in our centre was initial high resolution ultrasound with a minimum transducer frequency of 12.5MHz. ^{99m}Tc-sestamibi (Planar and SPECT/CT) was performed only where ultrasound failed to identify a source for autonomous PTH secretion or where ultrasound findings were equivocal. Latterly, four-dimensional CT (4DCT) was employed where ultrasound and ^{99m}Tc-sestamibi-SPECT CT failed to identify an adenoma. Results are presented separately for the ^{99m}Tc-sestamibi uptake component (either planar ^{99m}Tc-sestamibi or ^{99m}Tc-sestamibi SPECT) and the CT component of

concomitant ^{99m}Tc-sestamibi SPECT CT imaging. Planar ^{99m}Tc-sestamibi and ^{99m}Tc-sestamibi SPECT were considered as a single entity for data analysis. In cases with surgically confirmed adenoma/hyperplasia location data, the accuracy of imaging modalities were assessed in terms of ability to correctly lateralize disease and also to identify the precise location (i.e. right/left, superior/inferior or ectopic).

Pathology

Information on the location of the diseased parathyroid gland(s), dimensions, weight and ultimate histological subtype (adenoma, atypical adenoma, hyperplasia or carcinoma) was obtained from pathology reports. Tumour volume was calculated using the mathematical formula for the volume of an ellipsoid shape: $4/3 \times \pi \times a \times b \times c$ (where a, b and c are the radii of the 3 axes).

Statistics

Continuous variables were not normally distributed (assessed by Shapiro-Wilk test) and are reported as median (inter-quartile range). Comparisons between groups were analysed by Mann-Whitney U test or Kruskal-Wallis test (multiple groups). Categorical data were compared by Chi-square test. Correlations were analysed by Spearman rank test. Logistic regression analysis was employed to determine independent predictors of the presence of clinical features, recourse to neck imaging, failure of neck imaging and recourse to surgery. Statistical

significance was accepted at $p < 0.05$. All statistical analyses were performed on RStudio (version 1.1.338).

Results

Characteristics of cohort

The median age at diagnosis of PHPT was 68 years (IQR 58 – 77). The majority of patients (82.3%, n = 503) were female. Full baseline characteristics are presented in table 1.

22.7% (n = 139) presented with adjusted calcium greater than 0.25mM above the upper limit of normal (a level above which guidelines recommend surgery). 29.3% (171/584) had a phosphate below the reference range at presentation. 11.1% (n = 68) had a PTH within the reference range, 54.5% (n = 333) had PTH above normal but less than twice the upper limit of normal, and 34.4% (n = 210) had a PTH greater than twice the upper limit of normal. Only 1 of 251 (0.4%) surgically cured patients had a PTH < 5 pM at initial diagnosis (and only 1.8% of the total cohort). Vitamin D was available at baseline in 413 patients and was sufficient in 21.3% (n = 88), insufficient in 46.0% (n = 190) and deficient in 32.7% (n = 135). 18.5% of patients had chronic kidney disease (CKD) stage three, 0.5% had CKD4 and the remainder had normal renal function, as determined by eGFR.

Genetic testing was performed in 51 patients: MEN-1 (31 normal, 1 pathogenic mutation, 2 variants of uncertain significance); MEN-2 (22 normal, 0 pathogenic

mutations); CASR (10 normal, 1 pathogenic mutation) and CDC73 (12 normal, 1 pathogenic mutation).

Presenting symptoms

The most commonly reported symptoms at initial presentation were bone or joint pain, fatigue, polyuria, polydipsia, and constipation or abdominal pain (table 1). Low mood, memory impairment and weakness were less commonly recorded at diagnosis. 28.9% (176/610) reported no symptoms consistent with PHPT. Fatigue (2.88 [2.81 – 3.01] vs. 2.84 mM [2.73 – 2.98], P = 0.002) and weakness (2.94 [2.86 – 3.09] vs. 2.84 mM [2.75 – 2.98], P = 0.002] were associated with higher peak calcium but not PTH, adjusted calcium or calcium at presentation. Polydipsia was associated with higher adjusted calcium (2.77 [2.64 – 2.92] vs. 2.72 mM [2.65 – 2.82], P = 0.041), higher peak calcium (2.92 [2.81 – 3.06] vs. 2.84 [2.75 – 2.96], P < 0.001) and higher PTH (14.2 [10.8 – 21.1] vs. 12.0 pM [9.2 – 16.5], P = 0.002). Similarly polyuria was associated with higher adjusted calcium (2.76 [2.67 – 2.91] vs. 2.72 [2.65 – 2.83], P = 0.020) and peak calcium [2.89 [2.80 – 3.06] vs. 2.84 mM [2.75 – 2.96], P = 0.005). Constipation or abdominal pain was associated with higher presenting calcium (2.77 [2.68 – 2.90] vs. 2.73 [2.66 – 2.83], P = 0.016) but not peak calcium, adjusted calcium or PTH. Logistic regression analysis identified peak calcium (fatigue [OR 3.304, P = 0.028], polydipsia [OR 7.512, P = 0.012]) and PTH (polyuria [1.014, P = 0.045]) as being independently associated with symptoms; full analysis and logistic regression models are presented in section 1 of the

supplementary appendix. Memory impairment, depression and bone/joint pain were not independently associated with biochemical indices of PHPT.

Clinical features

Previous bone fracture was present in 16.4% (n = 100) at presentation with no significant clinical or biochemical (including PTH and calcium) associations observed (supplementary appendix section 2.A). A history of nephrolithiasis was present in 10.0% at initial presentation (n = 61) and was associated with higher adjusted calcium (2.80 [2.69 – 2.92] vs. 2.72 mM [2.64 – 2.82], P = 0.002) and PTH (13.2 [10.3 – 22.0] vs. 12.1 [9.3 – 16.7], P = 0.043), although in logistic regression analysis, younger age (OR 0.974, P = 0.006) and male gender (OR 1.972, P = 0.037), but not biochemical indices, were associated with the presence of renal stones at presentation (supplementary appendix 2.B). Cardiovascular disease was present in 16.7% (n = 102) at diagnosis of PHPT and hypertension in 43.5% (n = 266), neither were independently associated with biochemical indices of PHPT (supplementary appendix 2.C-D).

19.5% (n = 119) of patients were on a thiazide diuretic (specifically, bendroflumethazide) at diagnosis with no independently significant differences in biochemistry between thiazide treated and non-thiazide treated patients (supplementary appendix 2.E). Standard practice was to discontinue thiazide diuretics in all patients with PHPT. At 1 year follow up (n = 215 – no parathyroid surgery and 1 year data available) there was no significant difference in the

change in adjusted calcium: -0.01 [-0.11 - 0.06] in thiazide exposed vs. -0.04 mM [-0.11 – 0.04] with no previous thiazide, P = 0.514.

Correlation analyses

PTH was not correlated with age or BMI but was associated with adjusted calcium (R 0.350, P < 0.001), urinary CCCR (R 0.145, P < 0.05) and tumour volume (R 0.494, P < 0.001). A weaker association existed between tumour volume and adjusted calcium (R 0.246, P < 0.001). Vitamin D was only significantly inversely correlated with PTH (R -0.270, P < 0.001). The full correlation matrix is presented in table 2.

Discriminatory value of CCCR

CCCR was measured in 220 patients (36.0%). Urine CCCR did not differ significantly between individuals with vitamin D sufficiency (0.017 [0.009 – 0.024], n = 45), insufficiency (0.016 [0.009 – 0.020], n = 72) and deficiency (0.015 [0.009 – 0.021], n = 50, P = 0.612) (Figure 1). Similarly, urine CCCR did not significantly differ between spot urine samples (0.015 [0.010 – 0.023], n = 104] and 24-hour urine collection samples (0.016 [0.010 – 0.023], n = 116, P =0.239). CCCR was <0.01 in 18/99 (18.2%) surgically cured cases of PHPT and was <0.02 in 60/99 (60.6%).

Neck imaging

64.8% (n = 396) of patients received at least one modality of neck imaging. Independent predictors of neck imaging in this cohort included younger age (OR 0.912, P <0.001), higher adjusted calcium (OR 38.3, P < 0.001), lower phosphate (OR 0.05, P < 0.001), higher PTH (OR 1.03, P = 0.02) and presence of renal stones at presentation (OR 2.5, P = 0.046). The presence of osteoporosis or previous fracture was not associated with the decision to request neck imaging (full results presented in supplementary appendix section 3.A).

Neck ultrasound was performed in 61.2% of patients (n = 374), of whom an adenoma was reported as being identified in 66.0% (n = 247). Failure to identify an adenoma on ultrasound was associated with older age (66 [60 – 77] vs. 62 years [51 – 71], P < 0.001), lower peak calcium (2.86 [2.78 – 3.00] vs. 2.91 mM [2.82 – 3.05], P = 0.014), lower PTH (12.0 [8.7 – 16.6] vs. 14.0 pM [10.0 – 19.7], P = 0.006] and higher creatinine (72 [64 – 87] vs. 69μM [61 – 81], P = 0.022). Age (OR 0.963, P < 0.001), PTH (OR 1.027, P = 0.043) and creatinine (OR 0.989, P = 0.047), were all independently predictive in logistic regression analysis (presented in full in supplementary appendix section 3.B). The relationship with age remained present when the analysis was limited to patients with subsequent surgical cure (OR 0.963, P < 0.001) and so does not represent misdiagnosis of PHPT. Tumour volume and weight (at subsequent surgery) was not associated with the failure of ultrasound to detect an adenoma (supplementary appendix 3.B).

Where an adenoma was identified on ultrasound, the laterality was confirmed to be correct at surgery in 94.5% of cases (172/182). The corresponding figure for

sestamibi uptake was 66.1% (76/115); for the CT component of SPECT CT this was 83.3% (35/42). The number of 4DCT scans was substantially lower, but 7/10 adenomas reported were on the correct side at surgery. The full details of precise localisation (i.e. correct laterality and whether superior/inferior) are presented in table 3 for patients who had parathyroid surgery. The proportion of imaging studies which identified an adenoma and how this related to non-curative surgery are presented in table 4.

Delayed diagnosis and treatment

The interval between an elevated calcium and measurement of PTH was less than 1 year in 72.5% of patients (n = 443) but was between 1 – 5 years in 15.5% (n = 95) and greater than 5 years in 11.9% (n = 73). Patients with a delayed diagnosis were younger (62 [51 – 60] vs. 67 years [57 – 66], P = 0.004) and had lower initial adjusted calcium concentration (2.64 [2.59 – 2.72] vs. 2.76 [2.59 – 2.72], P < 0.001) but no difference in PTH (full results presented in supplementary appendix section 4).

Where the diagnosis of PHPT was made within 1 year, 26.1% received surgery within 1 year, 18.9% between 1 and 5 years and 1.6% beyond 5 years (no surgery in 53.4%). Where the diagnosis was made between 1 and 5 years, 31.2% received surgery within this timeframe and a further 7.5% received surgery beyond 5 years (no surgery in 61.3%). Where the diagnosis was delayed beyond 5 years, 38.3% received surgery (no surgery in 61.6%).

Features associated with having parathyroid surgery

44.8% of our patients (n = 274) had parathyroid surgery. Surgery was more likely in younger individuals (61 [50 – 70] vs. 74 years [66 – 81], P < 0.001), those with higher adjusted calcium (2.78 [2.68 – 2.92] vs. 2.70 mM [2.64 – 2.77], higher PTH (14.3 [10.0 – 20.2] vs. 11.4 pM [8.8 – 14.3], P < 0.001), where neck imaging identified an adenoma (OR 3.3, P < 0.001) and those with a history of nephrolithiasis (OR 1.80, P <0.001). Osteoporosis was not associated with a higher likelihood of having had surgery (OR 0.89, P = 0.273), although after adjusting for age, there was a borderline association between osteoporosis and greater likelihood of surgery (OR 1.60, P = 0.057). Logistic regression analysis confirmed identification of an adenoma on imaging (OR 10.7, P < 0.001), younger age (OR 0.92, P < 0.001), higher adjusted calcium (OR 15.3, P < 0.001) and history of nephrolithiasis (OR 3.1, P = 0.007) as being independently associated with the likelihood of surgery (full analysis presented in supplementary appendix section 5A-C).

Predictors of non-curative surgery

Surgery failed to cure PHPT in 8.4% of patients in our centre (23/274). There were no significant differences in pre-operative clinical and biochemical parameters between those with curative and non-curative surgery (supplementary appendix section 6). There was, however, an increased risk of non-curative surgery where more than one imaging modality was employed (OR 2.42, P = 0.035) and a trend towards higher likelihood of non-curative surgery in

patients where US failed to identify an adenoma (OR 2.3, P = 0.052). Of the 23 patients with non-curative surgery, 12 have had subsequent cure following reoperation. One further patient was subsequently diagnosed with FHH. Ultimately only 11/273 (4.0%) of patients with PHPT and surgical intervention had persistent PHPT.

Location of tumour and pathology

Where a precise location was specified following surgery (n = 199), the right inferior position was the commonest adenoma site (40.7%, n = 81), followed by left inferior (33.2%, n = 66), left superior (9.0%, n = 18), right superior (8.0%, n = 16), multiple sites (7.0%, n = 14) and, finally, ectopic (2.0%, n = 4). The full tumour location data is presented in section 7 of the supplementary appendix. The commonest pathological diagnosis was adenoma (79.8%, n = 205), followed by hyperplasia (12.8%, n = 33), carcinoma (4.3%, n = 11) and atypical adenoma (3.1%, n = 8). Calculated tumour volume (R 0.494, P < 0.001), maximum tumour dimension (R 0.438, P < 0.001) and tumour weight (0.424, P < 0.001) were all strongly correlated with PTH at diagnosis (figure 2).

Discussion

We have reported the largest detailed, consecutive series of patients presenting to a secondary care endocrine service for evaluation of PHPT. The results and conclusions drawn from this cohort are likely to be applicable to the majority of

endocrine centres across the United Kingdom and beyond. Whilst susceptible to the typical criticisms of retrospective studies, the strength of this evaluation is its reflection of 'real world' clinical practice over the past decade.

Symptoms

Asymptomatic PHPT is often a misnomer as most patients with PHPT describe symptoms which are at least consistent with hypercalcaemia. Previous studies of symptoms frequency have suggested over 90% of patients report at least one symptom[11,12]. These earlier studies were confined to patients awaiting parathyroid surgery and arguably represent the more severe end of the spectrum. The corresponding figure in our study was 71.1%, although because we did not use a prospective data collection tool this may reflect under-reporting. Whilst fatigue was relatively common in our patients (23.8%), this was significantly lower than earlier reports (35 – 40%)[11]. In contrast, our reported prevalence of bone pain and polyuria were broadly consistent with previous estimates. Consistent with earlier reports, fatigue and polyuria appeared to be the symptoms most closely associated with biochemical indices of PHPT severity[12].

Clinical features

There is little doubt that PHPT is associated with an increased risk of nephrolithiasis. Recent estimates of the lifetime risk of nephrolithiasis in the general population are 3 – 5% in women and 10 – 15% in men[13]. In our cohort,

at presentation, 8.5% of women and 16.7% of men had a prior history of renal stones. Interestingly, whilst univariate analysis demonstrated significantly higher adjusted calcium in those with renal stones, logistic regression identified only younger age and male gender as independent associations. Indeed, in women first presenting over the age of 65, the prevalence of renal stones is close to the upper end of prevalence estimates for the general population (5.4%, 16/295). This suggests that aggressive case finding, with respect to nephrolithiasis, may be unnecessary in older women, although this would require validation in other populations. That the presence of cardiovascular disease and hypertension were not associated with biochemical indices of PHPT is not surprising given the high prevalence of these conditions and the multifactorial contributions to their development[14]. Presence of previous fracture was also unrelated to presenting biochemistry again probably representing multifactorial contributions towards fracture risk.

Thiazides

As thiazide diuretics diminish urinary calcium excretion, received wisdom has been to discontinue this class of medication in patients diagnosed with PHPT, as this may reduce plasma calcium concentration. If thiazides do have a significant impact on plasma calcium we would have expected to see greater reduction in calcium at one year after their cessation in our non-surgical patients on thiazide diuretics at diagnosis (thiazides were discontinued in all patients in this cohort). However, no significant difference was observed lending further evidence to the

contention[9] that the diagnosis of PHPT should not lead to automatic discontinuation of thiazides.

CCCR

Our demonstration that baseline urinary CCCR is less than 0.01 in 18.2% of patients with surgically confirmed PHPT calls into question the usefulness of this investigation in differentiating PHPT from FHH. This frequency is broadly consistent with previous reports[15,16,17]. Yet the 4th international workshop on the diagnosis of PHPT[8] suggests a greater than 95% chance of FHH when CCCR is <0.01. This conclusion, which is commonplace in endocrine texts[18], is based on positive predictive value estimates performed in samples highly enriched with FHH cases, despite this being a substantially less common condition than PHPT (prevalence estimated at 1 in 78,000 in Scotland)[19]. PHPT remains by far the likeliest diagnosis in a hypercalcaemic patient with CCCR < 0.01.

It is also frequently suggested that vitamin D status may complicate the interpretation of urinary CCCR results[8]. However, we found no difference in urinary CCCR between vitamin D deficient, insufficient and replete individuals and no correlation existed between indices of urinary calcium excretion and plasma vitamin D. This lack of association is consistent with the observations in a small study of 35 PHPT patients[20] and also with the lack of effect upon urinary calcium excretion observed following vitamin D replacement in patients with PHPT[21].

We did not observe any difference in CCCR between 24-hour samples and spot urine samples, although 24-hour collections may be indicated for a full

assessment of urinary calcium excretion in line with the current international workshop guidance[6].

Imaging

Failure of imaging to identify an adenoma was independently associated with a lower likelihood of proceeding to surgery and, in those who had surgery, failure to cure PHPT was more likely where more than one imaging modality was required. These facts strongly support the need for more effective second-line imaging modalities, as even 4DCT was associated with an appreciable failure rate. This study cannot be regarded as a 'head to head' comparison of imaging modalities as only more complex cases were referred for imaging beyond neck ultrasound. As a proportion of all ultrasound scans with subsequent surgery, only 46.4% identified the precise location (including cases where no adenoma was identified) however 94.5% of scans where an adenoma was identified lateralized correctly. This compares to precise localisation in 78% [22], 74%[23], 61%[24] and 29%[25] in previous studies. Differences in rates of adenoma identification between this cohort and others may reflect different population characteristics, as we identified older age and lower PTH to be independent predictors of failure to identify an adenoma. Evidence is mixed with respect to whether ^{99m}Tc-sestamibi is a superior initial investigation[22-25] compared to ultrasound. Little difference appears to exist between planar ^{99m}Tc-sestamibi compared to ^{99m}Tc-sestamibi-SPECT[26], which supports our decision to consider these scans as a single entity in our analysis. 4DCT is reported to lateralise correctly in 88% of cases and provide precise localisation in 70%[25]. Although

the number of 4DCT results in our cohort was low, it suggests this investigation does not perform this well in selected difficult cases where earlier imaging modalities have failed to identify abnormal parathyroid gland(s). Recent experience with 18-fluorocholine PET/CT offers some hope that this modality may offer improved performance in difficult cases where conventional imaging has failed to identify a source for PTH excess[27].

Surgery

We have confirmed the findings of earlier investigators that the majority of parathyroid adenomas (>70%) occur in glands in the inferior position[28]. Previous reports have offered conflicting evidence on the relationship between PTH at diagnosis and adenoma size[29,30]. However our series, which is the largest to address this question, shows an unequivocal relationship with respect to both calculated adenoma volume and weight. The prevalence of parathyroid carcinoma (4.3%) was higher than is suggested elsewhere (<1% of cases of PHPT)[31] but this may be a consequence of referral bias *i.e.* 'milder' PHPT in older patients is less likely to be referred to secondary care and our population is therefore enriched with more severe disease. Otherwise the mix of pathological diagnoses is broadly in accord with the previous literature[1]. Non-curative surgery was most strongly associated with difficulties in identifying disease on neck imaging and this has been reported by other investigators previously[32]. Earlier reports also identified older age, higher calcium and lower PTH as risk factors for failed surgery[33]. Whilst our study was perhaps underpowered to reproduce these findings, trends were consistent with this larger series. Our

centre has not utilised intra-operative PTH assessment but this is a potentially attractive option, particularly in patients where risk factors for non-curative surgery are identified, to increase the likelihood of successful outcomes[34].

Delayed diagnosis

Over a quarter of patients in this cohort had a substantial delay between the first episode of hypercalcaemia and the diagnosis of PHPT, with 11.9% waiting over 5 years before PTH was measured. This is perhaps unsurprising given an earlier series where only 31% of hypercalcaemic patients had a PTH concentration assessed[4]. Although it is difficult to quantify the potential harm inherent in delayed diagnosis, younger patients were more likely to belong to this category and 38% of those with greater than 5 year delay ultimately received surgery. As well as exposure to symptoms and risk of classical PHPT complications, observational evidence associates elevated PTH with a greater risk of cardiovascular disease and mortality[35]. Whilst we cannot infer causation from these observational data, it seems prudent to ensure timely diagnosis and expeditious referral for treatment in those where surgery is indicated. Our data suggest the need for improved systems and greater education in helping non-specialists appropriately investigate patients with modest hypercalcaemia.

Summary

The insights gained from this cohort provide useful information on the most discriminant clinical features of PHPT and further reassurance that thiazide

diuretic use is safe in PHPT. This series also suggests additional caution is required in the interpretation of CCCR and perhaps greater recourse to genetic testing, particularly as the cost of this technology plummets. With respect to imaging, we have demonstrated that neck ultrasound, when an enlarged parathyroid gland is positively identified, is highly accurate in lateralizing disease. However, failure to identify an enlarged parathyroid, and the requirement for multiple imaging modalities, is a significant risk factor for non-curative surgery. Improved and novel imaging modalities are required to minimise the risk of unsuccessful surgery. Worryingly, it appears the delay in diagnosis of PHPT is unacceptably long in many patients, suggesting the need for better systems and better education for non-specialists to ensure prompt diagnosis and, where appropriate, treatment.

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Figure Legends

Figure 1: Urine CCCR presented across vitamin D categories. Horizontal line denotes 0.01 threshold (P = 0.612 between the three vitamin D categories). N/A not measured

Figure 2: Maximum tumour dimension (median +/- IQR) presented by PTH category at diagnosis (comparison across groups P < 0.001).

Table 1: Summary of presenting features in patients with PHPT.

	N	Reference range	Median (IQR)
Age at first high calcium (years)	611		66.3 (56.4 – 64.9)
Age at first PTH result (years)	611		68.0 (58.0 – 77.0)
Interval from high calcium to PTH measurement (months)	611		1 (0 – 18.5)
Weight (kg)	448		73.3 (62.0 – 74.6)
BMI (kg/m^2)	445		27.8 (24.2 – 28.4)
SIMD rank (out of 6976)	610		4347 (2337 – 6210)
Gender	611		503 (82.3%) female 108 (17.7%) male
Fatigue at presentation	610		145/610 (23.8%)
Weakness at presentation	610		29/610 (4.8%)
Memory impairment at presentation	610		61/610 (10%)
Depression at presentation	610		81/610 (13.4%)
Polydipsia at presentation	610		91/610 (14.9%)
Polyuria at presentation	610		95/610 (15.6%)
Bone / joint pain at presentation	610		168/610 (27.5%)
Previous fracture at presentation	611		100/611 (16.4%)
Constipation / abdominal pain at presentation	611		88/611 (14.4%)
Thiazide diuretic at presentation	611		119/611 (19.5%)
Previous/current lithium therapy	611		18/611 (2.9%)
Renal stones at or prior to diagnosis	611		61/611 (10.0%)
Cardiovascular disease at diagnosis	611		102/611 (16.7%)
Calcium (mM) at diagnosis	611	2.1 – 2.6	2.73 (2.66 – 2.84)
Adjusted calcium (mM) at diagnosis	611	2.1 – 2.6	2.72 (2.65 – 2.84)
Peak calcium (mM)	611	2.1 – 2.6	2.85 (2.75 – 2.99)
PTH at diagnosis (pM)	611	1.6 – 7.5	12.1 (9.3 – 17.2)
Vitamin D (nM)	413	>50	31 (22 – 48)
Phosphate at diagnosis (mM)	584	0.8 – 1.4	0.90 (0.77 – 1.01)
Magnesium (mM)	243	0.7 – 1.0	0.84 (0.73 – 0.91)
Creatinine (μM)	611	60 – 120	71 (63 – 87)
Alkaline phosphatase (U/L)	611	40 – 125	94 (78 – 114)
Urine calcium (mM)	334		3.6 (2.0 – 5.3)
Urine calcium (mmol/24hrs)	216	<7.5	6.1 (3.8 – 9.0)
Urine CCCR	220		0.0158 (0.0091 – 0.0213)

Table 2: Correlations between clinical and biochemical parameters in patients with PHPT (n = 611 unless stated otherwise).
Spearman correlation results above black boxes / P values below black boxes.

	BMI (n = 445)	Age	Adjusted Calcium	Phosphate (n = 584)	PTH	Vitamin D (n = 413)	Creatinine	Urine calcium per litre (n = 334)	CCCR (n = 220)	Tumour maximum dimension (n = 232)	Tumour weight (n = 213)	Tumour volume (n = 213)
BMI		-0.106	0.034	-0.185	0.027	-0.008	0.105	0.135	-0.059	-0.104	-0.026	-0.053
Age	0.026		0.024	0.106	0.047	-0.063	0.257	-0.239	-0.052	0.030	0.011	0.040
Adjusted calcium	0.468	0.557		-0.216	0.350	-0.019	0.026	0.137	0.125	0.254	0.230	0.246
Phosphate	<0.001	0.010	<0.001		-0.327	0.131	-0.052	-0.198	-0.044	-0.234	-0.256	-0.241
PTH	0.576	0.242	<0.001	<0.001		-0.270	0.070	0.122	0.145	0.438	0.424	0.494
Vitamin D	0.883	0.205	0.700	0.009	<0.001		0.035	-0.117	0.079	-0.003	-0.081	-0.056
Creatinine	0.026	<0.001	0.526	0.207	0.083	0.475		-0.261	-0.055	0.169	0.236	0.185
Urine calcium	0.028	<0.001	0.012	<0.001	0.026	0.072	<0.001		0.506	0.151	0.146	0.160
CCCR	0.423	0.444	0.065	0.526	0.031	0.310	0.413	<0.001		0.285	0.402	0.243
Tumour maximum dimension	0.197	0.646	<0.001	<0.001	<0.001	0.972	0.010	0.067	0.006		0.786	0.848
Tumour weight	0.756	0.869	<0.001	<0.001	<0.001	0.380	<0.001	0.090	<0.001	<0.001		0.821
Tumour volume	0.524	0.563	<0.001	<0.001	<0.001	0.538	0.007	0.062	0.022	<0.001	<0.001	

Table 3: Relationship between pre-operative imaging and ultimate surgical outcome.

	Ultrasound	^{99m}Tc-sestamibi uptake	SPECT CT location	4DCT
Correct location	116 (46.4%)	59 (42.8%)	30 (66.7%)	7 (53.8%)
Wrong location	18 (7.2%)	24 (17.4%)	8 (17.8%)	0 (0.0%)
No adenoma /uptake on imaging	56 (22.4%)	24 (17.4%)	7 (15.6%)	3 (23.1%)
No precise location reported by surgeon	48 (19.2%)	22 (15.9%)	0 (0.0%)	0 (0.0%)
No precise location reported by radiologist	0 (0.0%)	1 (0.72%)	0 (0.0%)	0 (0.0%)
No adenoma at surgery	5 (2.0%)	8 (5.8%)	0 (0.0%)	3 (23.1%)
Multiple tumours at surgery	7 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
TOTAL	250	138	45	13

Table 4: Presence of enlarged parathyroid on imaging, whether surgery was performed and ultimate outcome of surgery by imaging modality and number of modalities employed. Where ^{99m}Tc-sestamibi SPECT CT was performed this is considered as 2 modalities (CT and scintigraphy). Planar ^{99m}Tc-sestamibi and ^{99m}Tc-sestamibi SPECT are reported as a single category.

	1 modality	2 modalities	3 modalities	4 modalities	Tumour on scan?	Surgery done?	Surgery failed?
Thyroid US	168 (44.9%)	72 (19.2%)	121 (32.4%)	13 (3.5%)	247/374 (66.0%)	257/374 (68.7%)	20/257 (7.8%)
Sestamibi / Sestamibi SPECT	10 (4.5%)	76 (34.5%)	121 (55.0%)	13 (5.9%)	144/220 (65.5%)	137/220 (62.3%)	16/137 (11.7%)
SPECT CT	0 (0.0%)	2 (2.2%)	78 (83.9%)	13 (14.0%)	64/93 (68.8%)	59/93 (63.4%)	6/59 (10.2%)
4DCT	0	0	18 (60.0%)	12 (40.0%)	15/30 (50.0%)	13/30 (43.3%)	4/13 (30.8%)
Tumour on any scan?	166/181 (91.7%)	64/79 (81.0%)	99/121 (81.8%)	9/13 (69.2%)			
Surgery done?	140/181 (77.3%)	51/79 (64.6%)	75/121 (64.6%)	6/13 (46.2%)			
Surgery failed?	7/140 (5.0%)	7/51 (13.7%)	7/75 (7.9%)	2/6 (33.3%)			

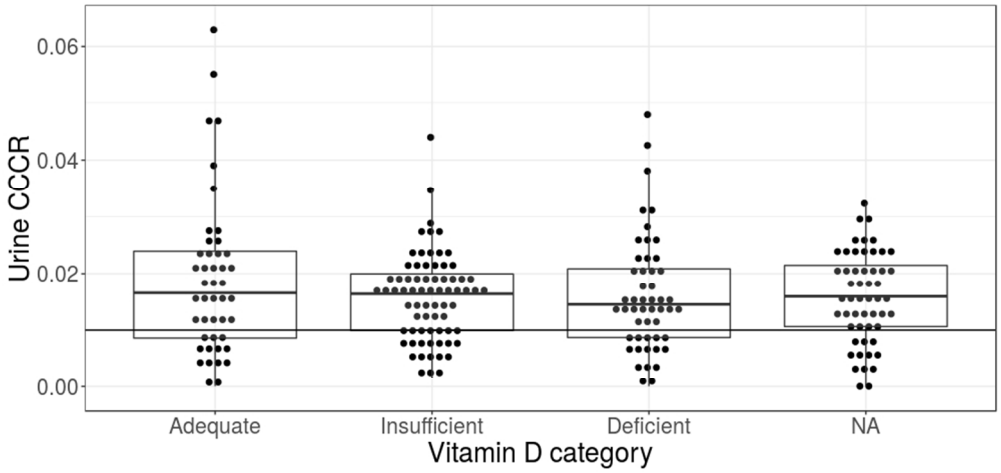

Figure 1: Urine CCCR presented across vitamin D categories. Horizontal line denotes 0.01 threshold (P = 0.612 between the three vitamin D categories). N/A not measured

264x125mm (96 x 96 DPI)

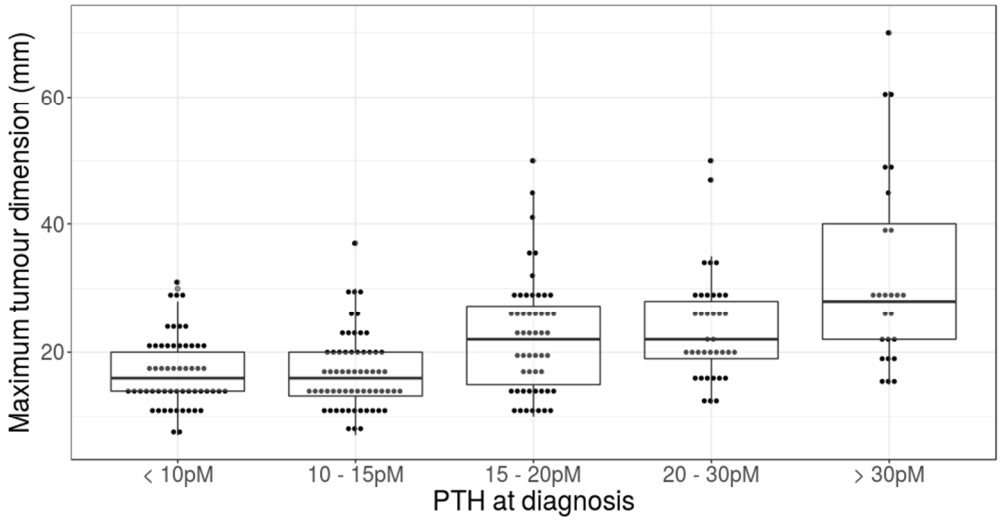

Figure 2: Maximum tumour dimension (median +/- IQR) presented by PTH category at diagnosis (comparison across groups P < 0.001).

264x138mm (96 x 96 DPI)